(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 September 2002 (12.09.2002)

PCT

(10) International Publication Number
WO 02/069968 A1

(51) International Patent Classification[7]: A61K 31/437, 31/4375, 45/00, 31/405, A61P 1/04, 29/00

(21) International Application Number: PCT/SE02/00375

(22) International Filing Date: 5 March 2002 (05.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0100798-8 8 March 2001 (08.03.2001) SE
0103291-1 3 October 2001 (03.10.2001) SE

(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **EEK, Arne** [SE/SE]; AstraZenaca R & D Södertälje, S-151 85 Södertälje (SE).

(74) Agent: **ASTRAZENECA AB**; Global Intellectual Property, S-151 85 Södertälje (SE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/069968 A1

(54) Title: NEW USE

(57) Abstract: The present invention relates to a new use of certain pharmaceutically active compounds in the treatment and/or prevention of medicament induced gastric ulcer. More particularly the invention is directed to the use of said compounds, and pharmaceutically acceptable salts thereof, for the treatment and/or prevention of NSAID (non-steroidal antiinflammatory drugs) induced gastric ulcer as well as a pharmaceutical composition in the unit dosage form for the prevention of NSAID induced gastric ulcer in a mammal comprising an NSAID together with a 6-carboxamido-imidazo[1,2-a]pyridine compounds. Other pharmaceutically active compounds used in the present invention comprises COX-2 inhibitors, NO-NSAIDs and bisphosphonates.

NEW USE

Field of the invention

The present invention relates to a new use of certain pharmaceutically active compounds in the treatment and/or prevention of medicament induced gastric ulcer. More particularly the invention is directed to the use of said compounds, and pharmaceutically acceptable salts thereof, for the treatment and/or prevention of NSAID (non-steroidal antiinflammatory drugs) induced gastric ulcer as well as a pharmaceutical composition in the unit dosage form for the prevention of NSAID induced gastric ulcer in a mammal comprising an NSAID together with a 6-carboxamido-imidazo[1,2-a]pyridine compounds.

Background of the invention and prior art

Certain pharmacological agents are known to be useful in exerting a cytoprotective effect on the gastrointestinal tract. This cytoprotective effect is manifest in the ability of such compounds to treat or prevent inflammatory diseases of the gastrointestinal tract, such as gastric ulcer, duodenal ulcer, gastritis, and intestinal inflammatory diseases, such as Crohn´s disease and inflammatory bowel disease.

These inflammatory diseases are known to be caused by a wide variety of agents present in the gastrointestinal tract which are known to attack the surfaces thereof, producing the inflammatory disease response. Such agents include microorganisms, bacterial toxins, certain pharmaceuticals and chemical agents and indeed gastric acid itself is capable of attacking the stomach lining and producing the inflammatory state.

NSAID are a class of compounds that are used to relieve some symptoms caused by arthritis, such as inflammation, swelling, stiffness, and joint pain. NSAIDs are also used to relieve other kinds of pain or to treat other painful conditions, such as gout attacks, bursitis, tendinitis, sprains, strains, or other injuries.

Any NSAID is known to cause side effects, especially when it is used for a long time or in large doses. One example of such side effects is induced gastric ulcer.

COX-2 inhibitors, the newest class of NSAIDS, work by blocking COX-2 enzyme which is involved in the inflammation pathway. By sparing COX-1 enzyme, gastrointestinal toxicity is reduced, but still present.

Nitric oxide (NO) is a molecule of versatility and importance in many guises. In the atmosphere it is a noxious chemical, but in the body in small and controlled doses it is extraordinary beneficial. It helps maintain blood pressure by dilating blood vessels, helps kill foreign invaders in the immune response, is a major biochemical mediator of penile erections, and is proposed to be a major biochemical component of long-term memory. Nitric oxide releasing NSAIDs (NO-NSAIDs) are disclosed in *e.g.* WO 94/04484.

Bishosphonates are a class of compounds well known for their therapeutic benefits in a variety of disorders associated with abnormal bone resorption, *e.g.* osteoporosis, Paget's desease, periprosthetic bone loss or osteolysis, metastatic bone disease, hypercalcemia of malignancy, multiple myeloma, periodontal desease and tooth loss. The most common of these disorders is osteoporosis, which in its most frequent manifestation occurs in postmenopausal woman. Examples of such bisphosphonate compounds is alendronate, risedronate, tiludronate, ibandronate, zoledronate and etidronate. Despite their therapeutic benefits, bisphosphonates are poorly absorbed from the gastrointestinal tract. If oral administration of the bisphosphonate is desired relatively high doses must be administered to compensate for the low bioavailability from the gastrointestinal tract. However oral administration of high doses of bisphosphonates are associated with adverse gastrointestinal effects, especially those relating to the esophagus. Pamidronate has for example been associated with esophageal ulcers, see E.G. Lufkin et al., Pamidronate: An Unrecognized Problem in Gastrointestinal Tolerability, Osteoporosis International, 4: 320-322 (1994).

For the treatment of ulcer disease, various drugs such as antacid, anticholinergic agent, Hz-receptor antagonist and proton pump inhibitor have been used. The commercial success of omeprazole has rekindled the interest in this field. The proton pump inhibition by omeprazole is irreversible and a reversible proton pump inhibitor has been suggested to have therapeutical benefits and thus attempts to develop a reversible proton pump inhibitor have been made. For example WO 96/05177 disclose certain 1,2,3,4-tetra-hydroisoquinolin-2-yl)pyrimidine compounds as a reversible proton pump inhibitor.

Further, tricyclic imidazo[1,2-a]pyridine compounds in WO 94/14795 have also been reported and pyrrolopyridazine compounds in EP 742 218.

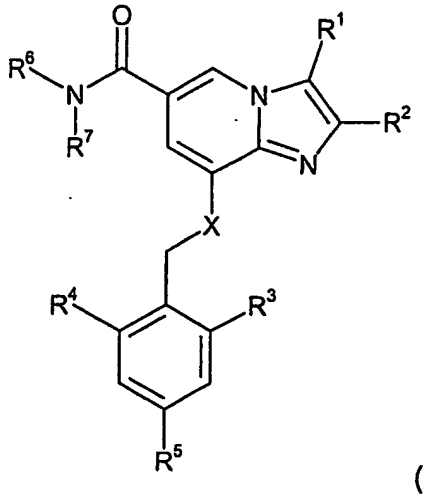
Certain 6-carboxamido-imidazo[1,2-a]pyridine compounds, as well as methods for producing said compounds, is described in WO 99/55706 and WO99/55705. Said compounds, and pharmaceutically acceptable salts thereof, is said to be effective in inhibiting secretion of gastric acid.

It has now surprisingly been found that certain pharmaceutically active compounds are useful in treatment and/or prevention of gastric ulcer induced by medicaments such as NSAID, COX-2 inhibitors, NO-NSAID and bisphosphonates.

Description of the invention

The present invention relates to the use of certain pharmaceutically active compounds in the treatment and/or prevention of medicament induced gastric ulcer. The present invention can thus be used to prevent a common side-effect affecting users of these pharmaceutically effective compounds. This is easiest done by co-administration of the two medicaments.

One object of the present invention is thus the use of certain 6-carboxamido-imidazo[1,2-a]pyridine compounds,as well as pharmaceutically acceptable salts thereof, of the general Formula I



(I)

wherein R^1 is

(a) H,

(b) CH_3, or

(c) CH_2OH;

R^2 is

(a) CH_3, or

(b) CH_2CH_3;

R^3 is

(a) H,

(b) C_1-C_6 alkyl,

(c) hydroxylated C_1-C_6 alkyl, or

(d) halogen;

R^4 is

(a) H,

(b) C_1-C_6 alkyl,

(c) hydroxylated C_1-C_6 alkyl, or

(d) halogen;

R^5 is

(a) H, or

(b) halogen;

R^6 and R^7 are independently selected substituents, containing C, H, N, O, S , Se , P and halogen atoms, which give compounds of Formula I a molecular weight ≤ 600,

X is

(a) NH, or

(b) O,

in the prevention of medicament induced gastric ulcer.

In a preferred embodiment of the present invention, R^1 is CH_3 or CH_2OH; R^2 is CH_3, R^3 is CH_3 or CH_2CH_3; R^4 is CH_3 or CH_2CH_3; R^5 is H, Br, Cl, or F; R^6 and R^7 are independently

(a) H,

(b) C_1–C_6 alkyl,

(c) hydroxylated C_1–C_6 alkyl,

(d) C_1–C_6 alkoxy-substituted C_1–C_6 alkyl,

(e) halogenated C_1–C_6 alkyl,

(f) aryl, in which aryl represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl, optionally substituted by one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, C_1–C_6 alkyl–NH–, $(C_1$–C_6 alkyl$)_2$–N–, or CN,

(g) aryl substituted C_1–C_6 alkyl, in which aryl represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl, optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, or OH,

(h) R^8–(C_1-C_6) alkyl-, wherein R^8 is NH_2C=O–, C_1–C_6 alkyl–NHC=O–, (C_1–C_6 alkyl$)_2$NC=O–, C_1–C_6 alkyl–OOC–, cyano, C_1–C_6 alkyl–CO–NH–, C_1–C_6 alkyl–OOCNH–, C_1–C_6 alkyl–O–, C_7-C_{12} alkyl-O- C_1–C_6 alkyl–SO–, C_1–C_6 alkyl–S–, C_1–C_6 alkyl–C=O–,-ArCONH–, Ar(C_1-C_6 alkyl)CONH, ArC=O–, NH_2CONH– C_1–C_6 alkyl–NHCONH–, (C_1–C_6 alkyl$)_2$–NCONH–, ArNHCONH–,hydroxylated C1-C6 alkyl-O- or morpholinyl ; wherein Ar represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, CN,

(i) C_7-C_{12} alkyl,

(j) OH,

(k) R^{11}-(C_1-C_6) alkyl-COO-(C_1-C_6) alkyl- wherein R^{11} is HOOC-, or C_1-C_6 alkyl -OOC-.

In a more preferred embodiment of the present invention, R^1 is

(a) H,

(b) CH_3, or

(c) CH_2OH;

R^2 is

(a) CH_3

(b) CH_2CH_3

R^3 is

(a) H

(b) C_1-C_6 alkyl,

(c) hydroxylated C_1-C_6 alkyl

(d) halogen

R^4 is

(a) H,

(b) C_1-C_6 alkyl,

(c) hydroxylated C_1-C_6 alkyl, or

(d) halogen;

R^5 is

(a) H, or

(b) halogen;

R^6, R^7 are the same or different

(a) H,

(b) C_1-C_6 alkyl;

(c) hydroxylated C_1-C_6 alkyl

(d) C_1-C_6 alkoxy-substituted C_1-C_6 alkyl

X is

(a) NH, or

(b) O.

In a more preferred embodiment of the present invention, R^1 and R^2 are CH_3, R^3 and R^4 are the same or different C_1-C_6 alkyl, R^5 is hydrogen, R^6 and R^7 are the same or different H, C_1-C_6 alkyl, hydroxylated C_1-C_6 alkyl, C_1-C_6 alkoxy-substituted or C_1-C_6 alkyl; and X is NH, or O.

As used herein, the term "C_1–C_6 alkyl" denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said C_1–C_6 alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

The term "halogen" includes fluoro, chloro, bromo and iodo.

The term "medicament induced gastric ulcer" consists of gastric ulcer induced or associated with the use of a medicament *e.g.* a medicant chosen from a group consisting of NSAID, COX-2 inhibitor, NO-NSAID, and bisphosphonates.

The term "prevent" or "prevention" is given its ordinary meaning and thus means the avoidance or alleviation of the serious consequences of a disease or a side-effect by early detection.

The pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers are within the scope of the invention. It should be understood that all the diastereomeric forms possible (pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers) are within the scope of the invention.

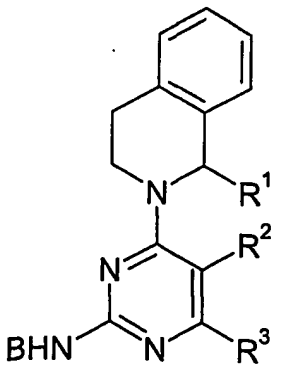
6-carboxamido-imidazo[1,2-a]pyridine of formula I above can thus be used in combination with NSAIDs and deliver the pharmaceutical effect of NSAID and surprisingly avoid the inherent noxious effect NSAIDS have on the stomach linen. It should be appreciated that there is no requirement that the components of the combination according to the present invention must be dosed simultaneously. Sequential or separate use of the components may also provide the desired beneficial effect. Where the administration is sequential, or separate, the delay in administering the second component should not be such as to lose the benefit of the synergistic effect of the combination. 6-carboxamido-imidazo[1,2-a]pyridine compounds of formula I can thus be administered simultaneously, sequentially or separately with an NSAID in therapy, e.g. for the treatment or prophylaxis of arthritis.

COX-2 inhibitors, the newest class of NSAIDS, work by blocking COX-2 enzyme which is involved in the inflammation pathway. By sparing COX-1 enzyme, gastrointestinal toxicity is reduced. A further aspect of the present invention is the combination of the 6-carboxamido-imidazo[1,2-a]pyridine compounds of formula I with COX-2 inhibitors in therapy e.g. for the treatment or prophylaxis of arthritis. Sequential or separate use of the components may also provide the desired beneficial effect. Where the administration is sequential, or separate, the delay in administering the second component should not be such as to lose the benefit of the synergistic effect of the combination. 6-carboxamido-imidazo[1,2-a]pyridine compounds of formula I can thus be administered simultaneously, sequentially or separately with a COX-2 inhibitor for the treatment or prophylaxis of e.g. arthritis.

Nitric oxide releasing NSAIDs (NO-NSAIDs) are disclosed in *e.g.* WO 94/04484. A further aspect of the present invention is the combination of the 6-carboxamido-imidazo[1,2-a]pyridine compounds of formula I with an NO-NSAID e.g. for the treatment or prophylaxis of pain. Sequential or separate use of the components may also provide the desired beneficial effect. Where the administration is sequential, or separate, the delay in administering the second component should not be such as to lose the benefit of the synergistic effect of the combination. 6-carboxamido-imidazo[1,2-a]pyridine compounds of formula I can thus be administered simultaneously, sequentially or separately with an NO-NSAID for the treatment or prophylaxis of pain.

A further aspect of the present invention is the combination of the 6-carboxamido-imidazo[1,2-a]pyridine compounds of formula I with bisphosphonates in therapy e.g. for the treatment or prophylaxis of osteoporosis. Sequential or separate use of the components may also provide the desired beneficial effect. Where the administration is sequential, or separate, the delay in administering the second component should not be such as to lose the benefit of the synergistic effect of the combination. 6-carboxamido-imidazo[1,2-a]pyridine compounds of formula I can thus be administered simultaneously, sequentially or separately with a bisphosphonate compound for the treatment or prophylaxis of e.g. osteoporosis.

Another object of the present invention is the use of certain 1,2,3,4-tetra-hydroisoquinolin-2-yl)pyrimidine compounds of formula II



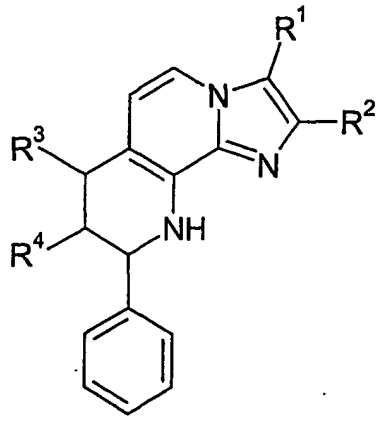
(II)

wherein R^1, R^2 and R^3 are independently selected from hydrogen or C_1-C_3 alkyl; and

B is C_1-C_3 alkyl, C_2-C_4 alkenyl, C_3-C_7 cycloalkyl, C_1-C_3 alkoxyethyl, substituted or un-substituted phenylethyl, 3-trifluoromethylphenylmethyl, 4-fluorophenyl, 1-naphthylmethyl, 4-methylthiazol-2-yl or 4-phenylthiazol-2-yl;
in the prevention of medicament induced gastric ulcer.

In a more preferred embodiment of the present invention, R^1, R^2 and R^3 of formula II are all methyl and B is 4-fluorophenyl.

Another object of the present invention is the use of certain tricyclic imidazo[1,2-a]pyridine compounds of formula III



(III)

wherein

R^1 is hydroxy C_1-C_4 alkyl;

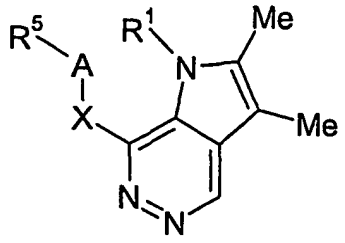
R^2 is C_1-C_4 alkyl;

R^3 and R^4 are independently selected from hydrogen, hydroxy, C_1-C_4 alkoxy, halogenated C_1-C_4 alkoxy, C_1-C_4 alkoxy-C_1-C_4 alkoxy, halogenated C_1-C_4 alkoxy-C_1-C_4 alkoxy, C_1-C_4 alkylcarbonyloxy, halogenated C_1-C_4 alkylcarbonyloxy, or carbonyl;
in the prevention of medicament induced gastric ulcer.

In a more preferred embodiment of the present invention R^1 is hydroxymethyl; R^2 is methyl;

R^3 and R^4 are independently selected from hydrogen, hydroxy, C_1-C_4 alkoxy or C_1-C_4 alkoxy-C_1-C_4 alkoxy.

Another object of the present invention is the use of certain pyrrolopyridazine compounds of formula IV



(IV)

wherein

R^1 is 1 -propenyl, 2-propenyl, 1 -butenyl, 2-butenyl, 2-methyl-2-propenyl, 3-phenyl-2-propenyl, cyclo-propylmethyl, or 2-methylcyclopropylmethyl;

R^5 is a phenyl group optionally substituted with halogen;

A is methylene; and

X is oxygen;

in the prevention of medicament induced gastric ulcer.

A more preferred embodiment of the present invention is the use of certain pyrrolopyridazine compounds of formula IV, wherein R^1 is 2-methylcyclopropylmethyl, and R^5 is a p-fluorophenyl, A is methylene; and X is oxygen.

Another object of the present invention is the use of the 6-carboxamido-imidazo[1,2-a]pyridine compounds of Formula I, as well as pharmaceutically acceptable salts thereof, for the manufacture of a medicament for the prevention of NSAID induced gastric ulcer.

Another object of the present invention is the use of a compound chosen from the group consisting of 6-carboxamido-imidazo[1,2-a]pyridine compounds of Formula I, 1,2,3,4-tetra-hydroisoquinolin-2-yl)pyrimidine compounds of formula II, tricyclic imidazo[1,2-a]pyridine compounds of formula III, and pyrrolopyridazine compounds of formula IV for the manufacture of a medicament for the prevention of medicament induced gastric ulcer.

Another object of the present invention is the simultaneous, separate or sequential co-administration of NSAID with the 6-carboxamido-imidazo[1,2-a]pyridine compounds of Formula I for the prevention of NSAID induced gastric ulcer.

Another object of the present invention is the simultaneous, separate or sequential co-administration of a medicament chosen from the group consisting of NSAID, COX-2 inhibitor, NO-NSAID or bisphosphonate with a compound chosen from the group consisting of 6-carboxamido-imidazo[1,2-a]pyridine compounds of Formula I, 1,2,3,4-tetra-hydroisoquinolin-2-yl)pyrimidine compounds of formula II, tricyclic imidazo[1,2-a]pyridine compounds of formula III, and pyrrolopyridazine compounds of formula IV for the prevention of medicament induced gastric ulcer.

Still a further object of the present invention is a method for the prevention of NSAID induced gastric ulcer, whereby an effective amount of the 6-carboxamido-imidazo[1,2-a]pyridine compounds of Formula 1, as well as pharmaceutically acceptable salts thereof, as active agent is administered simultaneous, separate or sequential with an NSAID to a mammal.

Still a further object of the present invention is a method for the prevention of medicament induced gastric ulcer, whereby an effective amount of a compound chosen from the group consisting of 6-carboxamido-imidazo[1,2-a]pyridine compounds of Formula I, 1,2,3,4-tetra-hydroisoquinolin-2-yl)pyrimidine compounds of formula II, tricyclic imidazo[1,2-a]pyridine compounds of formula III, and pyrrolopyridazine compounds of formula IV as active agent is administered simultaneous, separate or sequential with a medicament chosen from a group consisting of COX-2 inhibitor, NO-NSAID, and bisphosphonate to a mammal.

The present invention also relates to an oral pharmaceutical composition for simultaneous administration comprising an NSAID together with a 6-carboxamido-imidazo[1,2-a]pyridine compound of Formula I to prevent NSAID induced gastric ulcer in a mammal.

The present invention also relates to an oral pharmaceutical composition for simultaneous administration comprising a medicament chosen from a group consisting of NSAID, COX-2 inhibitor, NO-NSAID, and bisphosphonate together with a compound chosen from the

group consisting of 6-carboxamido-imidazo[1,2-a]pyridine compounds of Formula I, 1,2,3,4-tetra-hydroisoquinolin-2-yl)pyrimidine compounds of formula II, tricyclic imidazo[1,2-a]pyridine compounds of formula III, and pyrrolopyridazine compounds of formula IV to prevent medicament induced gastric ulcer in a mammal.

A pharmaceutical formulation comprising an medicament chosen from a group consisting of NSAID, COX-2 inhibitor, NO-NSAID, and bisphosphonate together with a compound chosen from the group consisting of 6-carboxamido-imidazo[1,2-a]pyridine compounds of Formula I, 1,2,3,4-tetra-hydroisoquinolin-2-yl)pyrimidine compounds of formula II, tricyclic imidazo[1,2-a]pyridine compounds of formula III, and pyrrolopyridazine compounds of formula IV as the pharmaceutical active ingredients, may contain further pharmaceutically acceptable carriers, diluents or adjuvants. The pharmaceutical formulation is preferable administered orally.

The amount of the pharmaceutical active ingredients in the pharmaceutical formulation to prevent medicament induced gastric ulcer is an amount which varies according to the mammal being treated, the severity of the disease, the included pharmaceutical active ingredients, and the route of administration selected. Usually the amount of pharmaceutical active ingredients are between 0.1-95% by weight of the preparation, preferably between 0.1-20% by weight in preparations for parenteral use and preferably between 0.1 and 50% by weight in preparations for oral administration.

The present invention also relates to an oral pharmaceutical composition for simultaneous administration comprising a COX-2 inhibitor together with a 6-carboxamido-imidazo[1,2-a]pyridine compound of Formula I in therapy, e.g. to prevent induced gastric ulcer in a mammal.

A pharmaceutical formulation comprising a COX-2 inhibitor together with the 6-carboxamido-imidazo[1,2-a]pyridine compound of Formula I as the pharmaceutical active ingredients, may contain further pharmaceutically acceptable carriers, diluents or adjuvants. The pharmaceutical formulation is preferable administered orally.

The present invention also relates to an oral pharmaceutical composition for simultaneous administration comprising an NO-NSAID together with a 6-carboxamido-imidazo[1,2-

a]pyridine compound of Formula I in therapy, e.g. to prevent induced gastric ulcer in a mammal.

A pharmaceutical formulation comprising a an NO-NSAID together with the 6-carboxamido-imidazo[1,2-a]pyridine compound of Formula I as the pharmaceutical active ingredients, may contain further pharmaceutically acceptable carriers, diluents or adjuvants. The pharmaceutical formulation is preferable administered orally.

The present invention also relates to a kit comprising a dosage unit of a compound chosen from the group consisting of 6-carboxamido-imidazo[1,2-a]pyridine compounds of Formula I, 1,2,3,4-tetra-hydroisoquinolin-2-yl)pyrimidine compounds of formula II, tricyclic imidazo[1,2-a]pyridine compounds of formula III, and pyrrolopyridazine compounds of formula IV and a dosage unit of a an NSAID, a COX-2 inhibitor, an NO-NSAID, or an bisphosphonate optionally with instructions for use.

Examples of NSAID to be used in the present invention include, but is not limited to,

Diclofenac,
Diflunisal,
Etodolac,
Fenoprofen,
Floctafenine,
Flurbiprofen,
Ibuprofen,
Indomethacin,
Ketoprofen,
Meclofenamate,
Mefenamic Acid,
Meloxicam,
Nabumetone,
Naproxen,
Oxaprozin,
Phenylbutazone,
Piroxicam,
Sulindac,
Tenoxicam,
Tiaprofenic Acid, and
Tolmetin

Examples of COX-2 inhibitors to be used in the present invention include, but is not limited to, Celebrex (Celecoxib), Vioxx (Rofecoxib).

Examples of NO-NSAID to be used in the present invention include, but is not limited to, those disclosed in WO 96/32946, WO 96/35416, WO 96/38136, WO 96/39409, WO

00/50037, US 6,057,347, WO 94/04484, WO 94/12463, WO 95/09831, WO 95/30641, WO 97/31654, WO 99/44595 and WO 99/45004.

Examples of bisphosphonates to be used in the present invention include, but are not limited to, alendronate, risedronate, tiludronate, ibandronate, zoledronate and etidronate.

The invention is illustrated, but in no way limited, by the following examples.

Examples

Groups of 10 male rats were given oral doses of vehicle, 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide(0.3, 1, 3 and 10 µmol/kg) or ranitidine (10 µmol/kg). Indomethacin 20 mg/kg, orally) was given 1 h after dosing. Stomach was removed 5 h after indomethacin and examined macroscopically

Results:

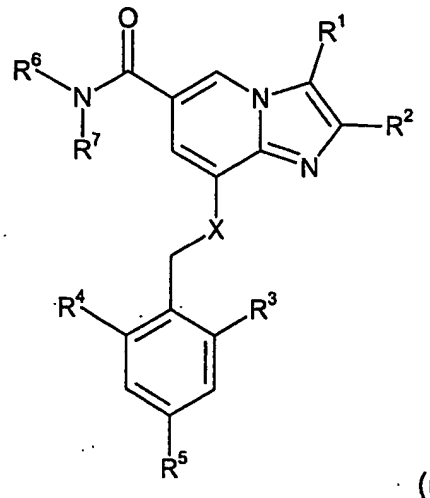
Indomethacin induced ulcers in the corpus only, rumen and anthrum were unaffected. Ulcers in the corpus were classified as pinhead (diameter 3 mm or less) or furrows (> 3 mm).
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide had a protective effect against gastric ulcers induced by indomethacin. This protective effect was dose-dependent and characterised by a decrease in the number of pinhead ulcers and ulcer furrows in the corpus. The decrease was statistically significant from the dose of 3 µmol/kg and maximal at 10 µmol/kg. Ranitidine had no effect.

Median number of gastric (corpus) ulcers induced by indomethacin

Group	Pinhead ulcers	Ulcer furrows
Vehicle	5	9
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide [0.3 µmol/kg]	5	8
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide [1 µmol/kg]	5	9
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide [3 µmol/kg]	2	1
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide [10 µmol/kg]	0	0
Ranitidine [10 µmol/kg]	7	11

CLAIMS

1. Use of a compound of formula I



(I)

or a pharmaceutically acceptable salt thereof, wherein R^1 is

(a) H,

(b) CH_3, or

(c) CH_2OH;

R^2 is

(a) CH_3, or

(b) CH_2CH_3;

R^3 is

(a) H,

(b) C_1-C_6 alkyl,

(c) hydroxylated C_1-C_6 alkyl, or

(d) halogen;

R^4 is

(a) H,

(b) C_1-C_6 alkyl,

(c) hydroxylated C_1-C_6 alkyl, or

(d) halogen;

R^5 is

(a) H, or

(b) halogen;

R^6 and R^7 are independently selected substituents, containing C, H, N, O, S , Se , P and halogen atoms, which give compounds of Formula I a molecular weight ≤ 600,

X is

(a) NH, or

(b) O,

in the prevention of medicament induced gastric ulcer.

2. Use according to claim 1 wherein R^1 is CH_3 or CH_2OH; R^2 is CH_3, R^3 is CH_3 or CH_2CH_3; R^4 is CH_3 or CH_2CH_3; R^5 is H, Br, Cl, or F; R^6 and R^7 are independently

(a) H,

(b) C_1–C_6 alkyl,

(c) hydroxylated C_1–C_6 alkyl,

~~(d)~~ C_1–C_6 alkoxy-substituted C_1–C_6 alkyl,

(e) halogenated C_1–C_6 alkyl,

(f) aryl, in which aryl represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl, optionally substituted by one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, C_1–C_6 alkyl–NH–, $(C_1$–C_6 alkyl$)_2$–N–, or CN,

~~(g)~~ aryl substituted C_1–C_6 alkyl, in which aryl represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl, optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, or OH,

~~(h)~~ R^8–(C_1-C_6) alkyl-, wherein R^8 is NH_2C=O–, C_1–C_6 alkyl–NHC=O–, $(C_1$–C_6 alkyl$)_2$NC=O–, C_1–C_6 alkyl–OOC–, cyano, C_1–C_6 alkyl–CO–NH–, C_1–C_6 alkyl–OOCNH–, C_1–C_6 alkyl–O–, C_7-C_{12} alkyl-O- C_1–C_6 alkyl–SO–, C_1–C_6 alkyl–S–, C_1–C_6 alkyl–C=O–,-ArCONH–, Ar(C_1-C_6 alkyl)CONH, ArC=O–, NH_2CONH– C_1–C_6 alkyl–NHCONH–, $(C_1$–C_6 alkyl$)_2$–NCONH–, ArNHCONH–,hydroxylated C1-C6 alkyl-O- or morpholinyl ; wherein Ar represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, CN,

(i) C_7-C_{12} alkyl,

(j) OH,

(k) R^{11}-(C_1-C_6) alkyl-COO-(C_1-C_6) alkyl- wherein R^{11} is HOOC-, or C_1-C_6 alkyl -OOC-.

3. Use according to claim 1 wherein R^1 is

(a) H,
(b) CH_3, or
(c) CH_2OH;

R^2 is

(a) CH_3
(b) CH_2CH_3

R^3 is

(a) H
(b) C_1-C_6 alkyl,
(c) hydroxylated C_1-C_6 alkyl
(d) halogen

R^4 is

(a) H,
(b) C_1-C_6 alkyl,
(c) hydroxylated C_1-C_6 alkyl, or
(d) halogen;

R^5 is

(a) H, or
(b) halogen;

R^6, R^7 are the same or different

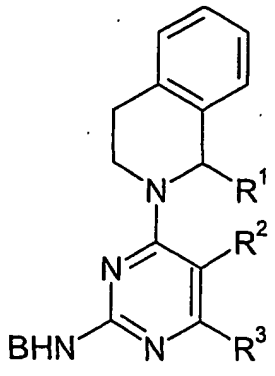
(a) H,
(b) C_1-C_6 alkyl;
(c) hydroxylated C_1-C_6 alkyl
(d) C_1-C_6 alkoxy-substituted C_1-C_6 alkyl

X is

(a) NH, or
(b) O.

4. Use according to claim 1, wherein R^1 and R^2 are CH_3, R^3 and R^4 are the same or different C_1-C_6 alkyl, R^5 is hydrogen, R^6 and R^7 are the same or different H, C_1-C_6 alkyl, hydroxylated C_1-C_6 alkyl, C_1-C_6 alkoxy-substituted or C_1-C_6 alkyl; and X is NH, or O.

5. Use of a compound of formula II,



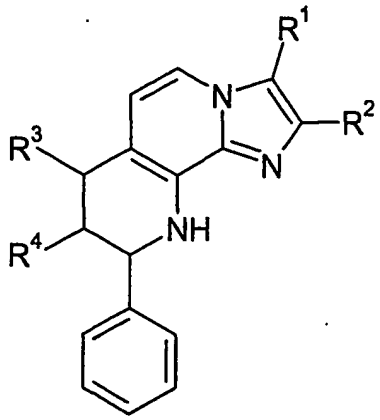
(II)

or a pharmaceutically acceptable salt thereof, wherein

R^1, R^2 and R^3 are independently selected from hydrogen or C_1-C_3 alkyl; and
B is C_1-C_3 alkyl, C_2-C_4 alkenyl, C_3-C_7 cycloalkyl, C_1-C_3 alkoxyethyl, substituted or unsubstituted phenylethyl, 3-trifluoromethylphenylmethyl, 4-fluorophenyl, 1-naphthylmethyl, 4-methylthiazol-2-yl or 4-phenylthiazol-2-yl;
in the prevention of medicament induced gastric ulcer.

6. Use according to claim 5, wherein R^1, R^2 and R^3 are all methyl and B is 4-fluorophenyl.

7. Use of a compound of formula III,



(III)

wherein

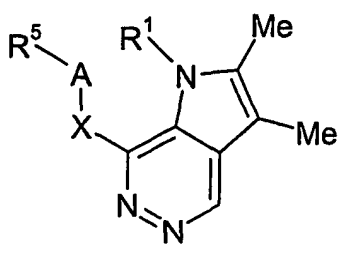
R^1 is hydroxy C_1-C_4 alkyl;

R^2 is C_1-C_4 alkyl;

R^3 and R^4 are independently selected from hydrogen, hydroxy, C_1-C_4 alkoxy, halogenated C_1-C_4 alkoxy, C_1-C_4 alkoxy-C_1-C_4 alkoxy, halogenated C_1-C_4 alkoxy-C_1-C_4 alkoxy, C_1-C_4 alkylcarbonyloxy, halogenated C_1-C_4 alkylcarbonyloxy, or carbonyl;
in the prevention of medicament induced gastric ulcer.

8. Use according to claim 7, wherein R^1 is hydroxymethyl; R^2 is methyl; R^3 and R^4 are independently selected from hydrogen, hydroxy, C_1-C_4 alkoxy or C_1-C_4 alkoxy-C_1-C_4 alkoxy.

9. Use of a compound of formula IV,



(IV)

wherein

R^1 is 1 -propenyl, 2-propenyl, 1 -butenyl, 2-butenyl, 2-methyl-2-propenyl, 3-phenyl-2-propenyl, cyclo-propylmethyl, or 2-methylcyclopropylmethyl;

R^5 is a phenyl group optionally substituted with halogen;
A is methylene; and
X is oxygen;
in the prevention of medicament induced gastric ulcer.

10. Use according to claim 9, wherein R^1 is 2-methylcyclopropylmethyl, and R^5 is a p-fluorophenyl, A is methylene; andX is oxygen.

11. A combination comprising a compound as defined in claims 1 to 10 and an NSAID for simultaneous, sequential or separate use in therapy.

12. A combination comprising a compound as defined in claims 1 to 10 and a COX-2 inhibitor for simultaneous, sequential or separate use in therapy.

13. A combination comprising a compound as defined in claims 1 to 10 and an NO-NSAID for simultaneous, sequential or separate use in therapy.

14. A combination comprising a compound as defined in claims 1 to 10 and a bisphosphonate for simultaneous, sequential or separate use in therapy.

15. A pharmaceutical formulation comprising the combination according to any one of claims 11 to 14 and a pharmaceutically acceptable carrier or diluent.

16. A first pharmaceutical formulation comprising a compound as defined in claims 1 to 10 and a pharmaceutically acceptable carrier or diluent; and a second pharmaceutical formulation comprising an NSAID, a COX-2 inhibitor, a bisphosphonate or an NO-NSAID and a pharmaceutically acceptable carrier or diluent.

17. A kit comprising a dosage unit of a compound as defined in claims 1 to 10 and a dosage unit of a an NSAID, a COX-2 inhibitor, an NO-NSAID or a bisphosphonate,

optionally with instructions for use.

18. Use of a compound of claims 1 to 10 for the manufacture of a medicament for the prevention of medicament induced gastric ulcer.

19. Method for prevention of medicament induced gastric ulcer, whereby an compound according to claim 1 to 10, as active agent is administered simultaneous, separate or sequential with an NSAID, a COX-2 inhibitor, an NO-NSAID or a bisphosphonate to a mammal.

20. An oral pharmaceutical composition in unit dosage form for the prevention of medicament induced gastric ulcer in a mammal comprising either an NSAID, a COX-2 inhibitor, an NO-NSAID or a bisphosphonate together with a compound of claims 1 to 10.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00375

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/437, A61K 31/4375, A61K 45/00, A61K 31/405, A61P 1/04, A61P 29/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9955706 A1 (ASTRA AKTIEBOLAG), 4 November 1999 (04.11.99), page 1, line 1 - line 7; page 17, line 19; the claims --	1-20
X	WO 9955705 A1 (ASTRA AKTIEBOLAG), 4 November 1999 (04.11.99), page 1, line 1 - line 7; page 18; the claimsj --	1-20
X	WO 9842707 A1 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH), 1 October 1998 (01.10.98) --	1-20
X	WO 0017200 A1 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH), 30 March 2000 (30.03.00) --	1-20

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 July 2002	02-07-2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00375

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0063211 A1 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH), 26 October 2000 (26.10.00)	1-20
A	EP 0033094 A1 (SCHERING CORPORATION), 5 August 1981 (05.08.81), page 73 - page 75	1-20
A	EP 0068378 A1 (SCHERING CORPORATION), 5 January 1983 (05.01.83), page 44, line 13 - page 46, line 24	1-20
A	Research Communications in Chemical Pathology and Pharmacology, vol. 57, no. 3, September 1987, Iwao Arai et al: "Effects of Indomethacin and cold-stress on gastric acid secretion and ulceration. The effects of anti-acid secretory agents in rats", page 313 - page 327, page 319 - page 320	1-20
A	EP 0465235 A1 (MCNEIL-PPC, INC.), 8 January 1992 (08.01.92)	1-20
A	EP 0550083 A1 (GLAXO GROUP LIMITED), 7 July 1993 (07.07.93)	1-20
A	EP 0426479 A1 (MCNEIL-PPC, INC.), 8 May 1991 (08.05.91)	1-20
A	US 3161654 A (TSUNG-YING SHEN), 15 December 1964 (15.12.64)	1-20

INTERNATIONAL SEARCH REPORT

Inte ıal application No.
PCT/SE02/00375

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-10,19
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet*

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see next sheet**

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

*

Claims 1-10,19 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

**

According to Article 34 (3) (a-c) and Rule 13.2, an international application shall relate to one invention only or to a group of inventions linked by one or more of the same or corresponding "special technical features", i.e. features that define a contribution which each of the inventions makes over the prior art.

The subjects defined by the names and structures listed below are so different from each other that no technical relationship or interaction is seen to be present so as to form a single general inventive concept.

Accordingly, the following inventions were found:

1. Use of a compound of the general formulae I or III according to claims 1-4, 7, 8 and 11-20 in part.

2. Use of a compound of the general formula II according to claims 5, 6 and 11-20 in part.

3. Use of a compound of the general formula IV according to claims 9,10 and 11-20 in part.

INTERNATIONAL SEARCH REPORT

Information on patent family members

10/06/02

International application No.
PCT/SE 02/00375

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9955706 A1	04/11/99	AU 727349 B	14/12/00
		AU 4300699 A	16/11/99
		AU 4300799 A	16/11/99
		AU 9098998 A	22/03/99
		BR 9909995 A	26/12/00
		BR 9909996 A	26/12/00
		CA 2329921 A	04/11/99
		CA 2329922 A	04/11/99
		CN 1306533 T	01/08/01
		CN 1307577 T	08/08/01
		EE 200000626 A	15/04/02
		EE 200000664 A	15/04/02
		EP 1011653 A	28/06/00
		EP 1073656 A	07/02/01
		EP 1073657 A	07/02/01
		HU 0102313 A	28/12/01
		HU 0102425 A	28/11/01
		JP 2001514215 T	11/09/01
		JP 2002513024 T	08/05/02
		JP 2002513025 T	08/05/02
		NO 20001087 A	02/03/00
		NO 20005450 A	22/12/00
		NO 20005451 A	27/12/00
		PL 338982 A	04/12/00
		PL 343797 A	10/09/01
		PL 343801 A	10/09/01
		SE 9801526 D	00/00/00
		SK 14912000 A	11/06/01
		SK 14922000 A	11/06/01
		TR 200003149 T	00/00/00
		TR 200003176 T	00/00/00
		US 6245818 B	12/06/01
		US 6313136 B	06/11/01
		US 6313137 B	06/11/01
		WO 9955705 A	04/11/99

INTERNATIONAL SEARCH REPORT

Information on patent family members

10/06/02

International application No.
PCT/SE 02/00375

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9955705 A1	04/11/99	AU 727349 B	14/12/00
		AU 4300699 A	16/11/99
		AU 4300799 A	16/11/99
		AU 9098998 A	22/03/99
		BR 9909995 A	26/12/00
		BR 9909996 A	26/12/00
		CA 2329921 A	04/11/99
		CA 2329922 A	04/11/99
		CN 1306533 T	01/08/01
		CN 1307577 T	08/08/01
		EE 200000626 A	15/04/02
		EE 200000664 A	15/04/02
		EP 1011653 A	28/06/00
		EP 1073656 A	07/02/01
		EP 1073657 A	07/02/01
		HU 0102313 A	28/12/01
		HU 0102425 A	28/11/01
		JP 2001514215 T	11/09/01
		JP 2002513024 T	08/05/02
		JP 2002513025 T	08/05/02
		NO 20001087 A	02/03/00
		NO 20005450 A	22/12/00
		NO 20005451 A	27/12/00
		PL 338982 A	04/12/00
		PL 343797 A	10/09/01
		PL 343801 A	10/09/01
		SE 9801526 D	00/00/00
		SK 14912000 A	11/06/01
		SK 14922000 A	11/06/01
		TR 200003149 T	00/00/00
		TR 200003176 T	00/00/00
		US 6245818 B	12/06/01
		US 6313136 B	06/11/01
		US 6313137 B	06/11/01
		WO 9955706 A	04/11/99
WO 9842707 A1	01/10/98	AU 740578 B	08/11/01
		AU 7520898 A	20/10/98
		BG 103696 A	30/06/00
		BR 9807883 A	22/02/00
		CN 1251102 T	19/04/00
		EE 9900450 A	17/04/00
		EP 0971922 A	19/01/00
		HR 980147 A	28/02/99
		HU 0001555 A	28/11/00
		IL 131407 D	00/00/00
		JP 2001518098 T	09/10/01
		NO 994584 A	23/11/99
		NZ 337325 A	29/06/01
		PL 335699 A	08/05/00
		SK 129799 A	16/05/00
		TR 9902257 T	00/00/00
		US 6197783 B	06/03/01

INTERNATIONAL SEARCH REPORT

Information on patent family members

10/06/02

International application No.
PCT/SE 02/00375

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0017200 A1	30/03/00	AU 6192099 A	10/04/00
		BG 105270 A	30/11/01
		BR 9914044 A	04/12/01
		CN 1319101 T	24/10/01
		CZ 20011082 A	12/09/01
		EP 1115725 A	18/07/01
		HR 20010224 A	30/04/02
		NO 20011243 A	12/03/01
		PL 346617 A	25/02/02
		SK 3992001 A	03/12/01
		TR 200100805 T	00/00/00
WO 0063211 A1	26/10/00	AU 3966600 A	02/11/00
		EP 1173439 A	23/01/02
EP 0033094 A1	05/08/81	SE 0033094 T3	
		AU 540840 B	06/12/84
		AU 6633781 A	30/07/81
		CA 1167845 A	22/05/84
		DE 3166531 D	00/00/00
		DK 25081 A	24/07/81
		ES 498643 A	16/11/82
		FI 810147 A	24/07/81
		GR 72960 A	19/01/84
		HK 94187 A	18/12/87
		HU 185857 B	28/04/85
		IE 50682 B	11/06/86
		IL 61939 A	31/01/86
		JP 56113782 A	07/09/81
		KR 8500240 B	12/03/85
		MY 76087 A	31/12/87
		NO 157781 B,C	08/02/88
		NO 810198 A	24/07/81
		NZ 196071 A	31/05/84
		OA 6727 A	30/06/82
		PT 72370 A,B	01/02/81
		SG 70887 G	04/03/88
		ZA 8100219 A	27/01/82

INTERNATIONAL SEARCH REPORT

Information on patent family members

10/06/02

International application No.
PCT/SE 02/00375

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0068378 A1	05/01/83	SE 0068378 T3	
		AT 18402 T	15/03/86
		AU 556062 B	23/10/86
		AU 8517882 A	06/01/83
		CA 1248957 A	17/01/89
		DE 3269604 D	00/00/00
		DK 284482 A	27/12/82
		ES 513431 A	01/08/83
		ES 8307806 A	01/11/83
		FI 73433 B,C	30/06/87
		FI 822266 A	27/12/82
		GR 74924 A	12/07/84
		HU 189595 B	28/07/86
		IE 53324 B	12/10/88
		IL 66141 D	00/00/00
		JP 1718718 C	14/12/92
		JP 4004318 B	27/01/92
		JP 58013584 A	26/01/83
		KR 8801718 B	08/09/88
		MY 62487 A	31/12/87
		NO 159724 B,C	24/10/88
		NO 822128 A	27/12/82
		NZ 201066 A	16/08/85
		OA 7130 A	31/03/84
		PH 20432 A	05/01/87
		PT 75115 A,B	01/07/82
		US 4450164 A	22/05/84
		ZA 8204516 A	29/02/84
		CA 1202630 A	01/04/86
		US 4507294 A	26/03/85
EP 0465235 A1	08/01/92	AU 8013991 A	09/01/92
		CA 2046074 A	04/01/92
		JP 4230330 A	19/08/92
		MX 9100080 A	28/02/92

INTERNATIONAL SEARCH REPORT

Information on patent family members

10/06/02

International application No.
PCT/SE 02/00375

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0550083 A1	07/07/93	AP 324 A	07/03/94
		AP 9200453 D	00/00/00
		AT 240692 A	15/02/96
		AT 401468 B	25/09/96
		AU 664574 B	23/11/95
		AU 2986392 A	10/06/93
		BE 1007268 A	09/05/95
		CA 2084568 A	07/06/93
		CH 685537 A	15/08/95
		CZ 9203580 A	13/10/93
		DE 69228738 D	00/00/00
		DK 550083 T	11/10/99
		ES 2130152 T	01/07/99
		FR 2684554 A,B	11/06/93
		GB 2262036 A,B	09/06/93
		GB 9126027 D	00/00/00
		GB 9225174 D	00/00/00
		GR 3030426 T	30/09/99
		IE 922866 A	16/06/93
		IL 103978 A	15/06/98
		IT 1256697 B	12/12/95
		IT RM920869 D	00/00/00
		JP 5246853 A	24/09/93
		LU 88196 A	17/08/93
		MX 9207008 A	01/06/93
		NO 924704 A	07/06/93
		NZ 245365 A	24/06/97
		US 5466436 A	14/11/95
		ZA 9209425 A	09/08/93
		GB 9206083 D	00/00/00
		RU 2134579 C	20/08/99
EP 0426479 A1	08/05/91	AT 101515 T	15/03/94
		AU 646230 B	17/02/94
		AU 6568990 A	09/05/91
		CA 2028746 A,C	03/05/91
		DE 69006684 D,T	09/06/94
		ES 2057439 T	16/10/94
		GR 1002097 B	28/12/95
		GR 90100786 A	17/04/92
		IE 64953 B	20/09/95
		IE 903946 A	08/05/91
		IN 171746 A	26/12/92
		JP 3206052 A	09/09/91
		NZ 235877 A	25/09/92
		PT 95753 A	30/09/91
		US 5204118 A	20/04/93
		US 5417980 A	23/05/95
		ZA 9008775 A	29/07/92
US 3161654 A	15/12/64	NONE	